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ORIGINAL ARTICLES

Which factors actually influence the development and progression of overt nephropathy in Nigerian diabetics?

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Abstract

Objective: To determine the risk factors predisposing Nigerian diabetics to overt nephropathy with a view to developing strategies for its prevention.
Design: case control study.
Setting: Tertiary care hospital, a major nephrology referral centre in Nigeria.
Subjects: 30 diabetic nephropathy (DN) patients and 32 age and sex-matched diabetic patients without nephropathy.
Materials and Methods: 30 diabetic nephropathy (DN) patients with chronic renal failure who have been diabetic for a minimum of five years and satisfied the inclusion criteria for the study were compared with 32 age and sex-matched diabetic patients without nephropathy. Their socio-demographic parameters, clinical and laboratory profiles were determined and compared. Results were analysed using the statistical package for social sciences version 10. Chi-square test, logistic regression analysis and Spearman's rank correlation coefficient were used, p-value<0.05 was considered as significant.
Main Outcome Measures: The study sought to compare socio-demographic, clinical and biochemical data between diabetic patients with overt nephropathy and those without.
Results: Duration of diabetes, blood pressures and blood sugar levels were significantly higher in DN patients than the controls (p<0.05). A family history of renal disease, socio-economic status, cigarette smoking, body mass index and total serum cholesterol did not distinguish between DN patients from controls (p>0.05). Systolic blood pressure positively correlated with serum creatinine (r=0.057, p<0.001) and duration of DM (r=0.284, p=0.02). There was a constellation of clinical features viz: retinopathy, peripheral neuropathy and left ventricular hypertrophy, which were significantly associated with DN (p<0.05).
Conclusions: Prolonged duration of diabetes, hypertension, retinopathy, and peripheral neuropathy, left ventricular hypertrophy and poor glycaemic control were the major risk factors for overt nephropathy among Nigerian diabetics. A preventive strategy should include adequate blood pressure and glycaemic control.

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Introduction

Diabetes mellitus (DM) is the commonest endocrine disease in the world, with a worldwide prevalence of 4% in adults.[1] In Nigeria the prevalence of DM ranges from 2.4 to 6% and varies from relatively rural to urban communities.[2] One of the most serious complications of DM is diabetic nephropathy (DN) with a prevalence of about 40%.[3] Unlike the previous reports which documented the rarity of diabetic nephropathy amongst Nigerians[4-11], it is now a leading cause of end stage renal disease (ESRD) in the world, as it accounts for about half of the total population of patients recruited to renal replacement treatment programmes in the western world.[12] Even locally, the prevalence of DN had increased significantly in the last 15 years from almost 0% of the causes of chronic renal failure to the third commonest cause accounting for 3 to 5% of the causes of ESRD.[3,13]

Diabetic ESRD causes severe morbidity and high mortality and the management is cost-intensive.[14] DN progresses through five recognised phases, which include the stage of hyperfiltration, during which the kidneys hypertrophy and the glomerular filtration rate (GFR) increases significantly with a resultant relatively low serum creatinine. During the next stage, described as the quiescent (silent) phase, the GFR and serum creatinine normalises. The third stage is that of microalbuminuria or incipient nephropathy stage during which spillage of microalbumin in urine occurs and is followed by the overt nephropathy stage during which macroalbuminuria occurs, along with development of hypertension and progressive diminution in GFR with a concomitant increase in serum creatinine. The last and final stage is end stage renal disease during which the patients are overtly uraemic and need renal replacement therapy for their survival. While the transition from one stage to the other could be discerned in type I diabetics, its rather blurred in type II disease which is the commonest type found in our environment. The implication of this is that the majority of our diabetics, particularly type II, could actually have progressed to incipient or overt nephropathy even before or at presentation. This was the findings of both Ikem, *et al*[15] and Alebiosu, *et al*[16] in south western Nigeria.

Diabetic nephropathy, once established, almost always progresses to end-stage renal disease (ESRD). Fortunately, not all diabetic patients develop nephropathy. Indeed, a subset of diabetic patients appears less prone to nephropathy despite long years of diabetes, suggesting the existence of some predisposing factors, which are either inherent or acquired.[16-21]

A number of factors have been identified among diabetic patient populations that induce and promote the development of nephropathy. While some are not modifiable, quite a lot of them can be controlled, managed or modified to reduce the progression of the disease. These non modifiable ones include genetic and/or familial predisposition, race, gender, ageing and age of onset as well as duration of DM.[17-21]

Genetic factors have, for a long time, been recognised as predisposing to nephropathy. There is familial clustering of nephropathy in diabetic siblings. While DN was present in 83% of probands with nephropathy, it was only 17% in probands without nephropathy. Amongst Pima Indians with diabetes, the incidence of proteinuria was 14%, if neither parent had proteinuria; 23% if one diabetic parent had proteinuria and 46% if both parents had proteinuria. Angiotensin gene polymorphism is also recognised as influencing a predisposition to nephropathy with subjects having DD phenotype being worst hit.[17-20]

Racial predilection is also recognised as predisposing to nephropathy. While there is a six fold increase in risk of ESRD in Mexican Americans and American Indians compared with whites, the risk is only 2.6 times higher in African-Americans when compared with the white population.[18-21]

The duration of diabetes also influences the evolution and progression of nephropathy. While DN rarely develops in the first five years of diabetes, it is uncommon after 15 years. Krowleski, *et al.* found that DN increased rapidly during the second decade of DM and later decreased. Hence the duration of DM could significantly impact on the development of nephropathy.

The modifiable risk factors include socio-economic factors, increased body mass index, cigarette smoking, hypertension, poor glycaemic control and hyperlipidaemia and/or dyslipidaemia.[21-27]
Hypertension confers worsening of prognosis in diabetics. It favours rapid evolution and progression of glomerulosclerosis and ESRD in patients with DN. Its development contributes to progressive decline of the glomerular filtration rate, rising serum creatinine and worsening of proteinuria.[15,25]

The benefits derived from good glycaemic control were exemplified by the results of the dialysis complications and control trial (DCCT), which showed a 56% reduction in the risk of worsening of microalbuminuria and clinical albuminuria (progression of nephropathy) and 43% reduced risk of developing microalbuminuria in subjects on intensive insulin therapy.[26]

These recognised risk factors act either singly or in concert to induce or promote nephropathy. If the factors predisposing to nephropathy are identified in the Nigerian diabetic population, it might be possible to develop a preventive strategy that will reduce the burden of diabetic ESRD in the country, so as not to have an epidemic of diabetic nephropathy similar to that currently being experienced in the west.

We, therefore, conducted this prospective case-control study to identify the risk factors predisposing to diabetic nephropathy and its progression to ESRD with a view to developing strategies for its prevention.

Materials and Methods

Thirty consecutive DN patients referred to the renal unit over a 12 month period (between September 2002 and August 2003) were recruited according to the following inclusion criteria:

1. Verified history of DM of duration ≥ 5 years.
2. A positive dipstick proteinuria ≥1+ in three early morning urine specimens.
3. Serum creatinine concentration ≥ 220μmol/L (2.5 mg%) and creatinine clearance < 30 ml/min.
4. DM prior to renal disease with no history of renal disease preceding DM.

Exclusion criteria were: pregnancy, congestive cardiac failure, evidence of urinary tract infection and unwillingness to participate in the study.

Thirty two consecutive DM patients without overt nephropathy, who were of comparable age and sex distribution to those with DN were selected from the prevalent diabetic patients that were attending the endocrine clinic of the hospital according to the following inclusion criteria:

1. Verified history of DM of duration ≥ 5years.
2. Negative dipstick proteinuria in 3 early morning urine samples.
3. Serum creatinine ≤132 mmol/l and creatinine Clearance >88 ml/min.

Exclusion criteria were: pregnancy, and refusal of consent.

Table I:Socio-demographic and clinical profiles of patients and controls.

Parameters	Patients	Controls	p value
Mean age (years)	43.36±7.10	41.53±4.18	NS
M:F ratio	1.71	1.28	NS
DM duration (years	12.56±4.29	9.93±3.29	0.009
Type 2 DM	22 (74%)	29 (90%)	NS
% Educated	22 (73.3%)	27 (85%)	NS
% Smokers	3 (13.3%)	1 (3.1%)	NS
BMI	23.91±3.21	23.37±3.2	NS
% with FHRD	2 (6.7%)	3 (9.4%)	NS
% with Neuropathy	26 (86.7%)	15 (46.9%)	NS
SBP (mmHg)	167.86±9.73	136.75±12.29	<0.001
DBP (mmHg)	91.33±13.12	83.65±11.0	0.016
% LVH	26 (86.7)	15 (46.9%)	<0.001
T-cholesterol (mmol/l)	5.06±0.65	4.90±0.63	NS
FBS (mmol/l)	8.55±4.45	6.70±1.78	0.01
2 hr PP Glucose (mmol/l)	10.14±3.41	8.32±1.93	0.01
SeCr (mmol/l)	777.3±32	100.93±20.0	<0.001

FHRD = Family history of renal disease; SeCr = Serum creatinine

The following parameters were studied: age at DM onset, gender, socio-economic status, duration of DM, and family history of renal disease, smoking status, body mass index, blood pressure, level of glycaemic control, serum total cholesterol, presence of co-morbidity (retinopathy, peripheral neuropathy and left ventricular hypertrophy).

A detailed history was obtained from each patient noting occupation and level of educational, age when diabetes was first diagnosed, history of cigarette smoking, family history of diabetes, renal disease and hypertension, and the antidiabetic and antihypertensive medications administered. A history of treatment with angiotensin-converting enzyme inhibitor was particularly sought.

A comprehensive general physical examination was carried out paying particular attention to the cardiovascular system, the nervous system, and the eyes.

Body weight was measured in kilogrammes with the patient in his or her light clothing using a standing or sitting scale. Heights were measured in metres with a standard ruler. Body mass index (BMI) was calculated from body weight (BW) and height measurements using the formula: BMI (Kg/m^2) = BW (kg)/Height x Height (m^2).

Retinopathy was assessed through an ophthalmologic examination using a Keeler's ophthalmoscope, with the pupils fully dilated.

Diabetic retinopathy[28] was classified as:

1. Background or nonproliferative retinopathy if there was evidence of microaneurysm, dot and blot haemorrhages or hard exudates.
2. Proliferative retinopathy, if there was evidence of neovascularisation, vitreal detachment, and retinal Haemorrhages.

The presence or absence of cataract was also noted. Hypertensive retinopathy was classified using the Keith-Wagener-Baker classification.[29] Nervous system examination included a full assessment of the cranial nerves, the reflexes and an evaluation for sensory or motor impairment.

Blood pressure was measured in the supine and standing positions using a mercury sphygmomanometer with a standard adult cuff (12cm x25cm) applied firmly on the left arm. Measurements were taken after the patient had sat comfortably for about five minutes. Patients with blood pressure persistently higher than 140/90 mm Hg on three consecutive clinical readings or patients currently on anti-hypertensive medication were considered hypertensive.

Left ventricular hypertrophy was determined clinically by the position of the cardiac apex on precordial examination, and by electrocardiography, using the Sokolow-Lyon criteria ($R_{V5\ or\ V6} + S_{V1\ or\ V2} \geq 35$ mm).[30]

Peripheral neuropathy was determined by impairment of pinprick and joint position sensation at the dorsum of the great toe, and vibration sense using a 128-Hz tuning fork.

After careful instructions, a 24 hour urine specimen collection was obtained from all patients and controls. Midstream, clean-catch urine culture was also done to rule out the presence of urinary tract infection. Patients with urine white blood cells of more than five per ml were treated and excluded from the study.

Fresh urine obtained from each patient on at least three occasions was used for dipstick protein examination (Albustix test) and the results recorded. Urinary and serum creatinine concentrations were measured colorimetrically using the alkaline picrate method (Jaffe reaction). This technique measures 'total creatinine' which includes non-creatinine chromogens in the serum.

Creatinine clearance was calculated using standard formula. Blood glucose and serum cholesterol concentration were also determined using standard methods.

Statistical Analysis.

The sample size (n) will be determined using the formula:-

$$n = (1.96)^2 \times \frac{P(I - P)}{d^2}$$

P =Prevalence rate of DM in Nigeria is 2.4% and only about 50% will develop nephropathy hence P=1.2%[2].

d =Tolerable sampling error (0.05)

Hence calculated sample size = 18 though 30 subjects were studied.

The Statistical Package for Social Sciences version 10 computer programme was used for the analysis. Results were expressed as absolute numbers, percentages, means with standard deviations, and range as appropriate. Chi-square and Fishers exact tests were used as appropriate to test significance of the difference of parameters between the groups. Logistic regression analysis was used to identify the risk factors. Spearman's rank correlation coefficient was used to test the association of some of the parameters with each other. A p value of <0.05 was considered as significant.

Table II: Logistic regression analysis for the risk factors for development of nephropathy.

Risk factors	Odds ratio	95% Confidence Interval	p value
Duration of DM	6.783	-0.346 - -0.074	0.009
Systolic Blood Pressure	32.723	-0.217 - -0.086	0.0001
Diastolic Blood Pressure	13.736	-0.209 - -0.094	0.0001
Fasting Blood Sugar	6.609	0.103 - 2.137	0.010
2hr-PP Blood Sugar	6.296	0.114 - 2.136	0.012
Diabetic retinopathy	17.78	-0.264 - -0.069	0.003
Peripheral neuropathy	10.946	0.109 - 2.142	0.01
Left ventricular hypertrophy	16.742	-0.198 - -0.024	0.009
BMI	0.496	-0.172 - 0.428	0.481
Total serum cholesterol	1.054	-0.41 - 0.20	0.305

Results

There were 30 DN subjects (18 males and 12 females) aged 20 to 57 years (mean 42.36 ± 7.1), and 32 controls (17 males and 15 females) aged 35 to 52 years (mean 41.53 ± 4.1). Duration of DM ranged from five to 21 years (mean 12.5 ± 4.2) in studied subjects and six to 21 years (mean 9.9 ± 3.2) in controls. Twenty two (74%) DN subjects had type II DM while that for the controls was 29 (90%) (p>0.05). Twenty two (73.3%) studied subjects and 27 (85%) controls had attained only primary a level of education (p>0.05). Trading was the most frequent occupation occurring in a similar proportion (25%) in studied subjects and controls (p=0.57). A positive family history of renal disease was obtained in three (9.4%) controls and two (6.7%) of the studied subjects (p>0.05). A history of cigarette smoking was strikingly low; it was positive in three (13%) of the studied subjects and in only one (3%) control (p=0.14). BMI ranged from 19 to 31 Kg/m^2 (mean 23. 91 ± 3.21) and 18 to 31 (mean 23.34 ± 3.23) in studied subjects and controls respectively (p>0.05). The blood pressure levels exhibited significant differences, with SBP ranging from 128 to 192 mm Hg (mean 167.86 ± 9.73) in studied subjects and 110 to 160 mm Hg (mean 136.75 ± 12.29) in controls (p<0.001). Also, DBP ranged between 70 to 130 mm Hg (mean 96.96 ± 14.24) in studied subjects and 60 to 105 mm Hg (mean 83.65 ± 11.00) in controls (p=0.01). While diabetic retinopathy was present in 22 (80.9%) of the studied subjects, it occurred only in seven (25.6%) controls (p=0.001). Hypertensive retinopathy of grade two to three by Keith-Wagner-Baker classification was present in 21 (70%) of the studied subjects and in 13 (40%) controls (p=0.01). Peripheral neuropathy was present in 26 (86.7%) patients and 15 (46.9% controls (p=0.001). FBS ranged from 4.1 to 19.1 mmol/l (mean 8.55 ± 4.1) in studied subjects and 3.8 to 12.6 mmol/l (mean 6.7 ± 1.78) in controls (p=0.01). Two hour post-prandial blood sugar (2h-PPBS) ranged from 5.8-20.5 mmol/l (mean 10.14 ± 3. 41) in studied subjects and six to 15mmol (mean 8.32 ± 1.93) in controls (p=0.01). Total serum cholesterol levels did not differ significantly between studied subjects and controls; the mean levels being 5.06 ± 0.65 mmol/l and 4.90 ± 0.53 mmol/l in studied subjects and controls respectively (p=0.21). Serum creatinine ranged from 252 to 1603 □mol/l (mean 773.3 ± 320) in studied subjects and 60 to 131 □mol/l (mean 100.93 ± 20.0) in controls. Creatinine clearance ranged from three to 34 ml/min (mean 13.52 ± 9.73) in studied subjects and 88 to 102 ml/min (mean 94.34 ± 12.06) in controls. LVH was present in 26 (86.7%) subjects and 15 (46.9%) controls (p<0.001). SBP was positively correlated with serum creatinine (r=0.057, p<0.001) (Figure I) and duration of DM (r=0.284, p=0.02) (Figure II).

Figure I: The relationship between SBP and duration of DM. R=0.284; p=0.025

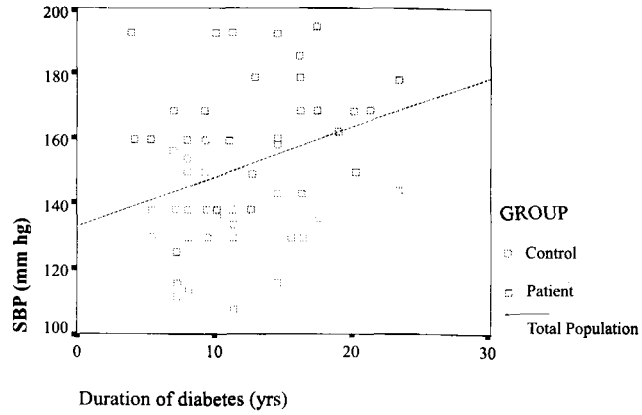
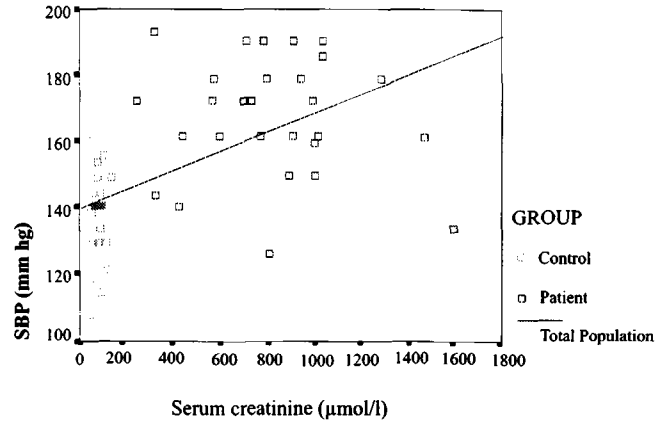


Figure II: Correlation between SBP (mm Hg) and serum creatinine (μmol/l) R=0.0577; p<0.001



Discussion

Diabetic nephropathy is a leading cause of end stage renal disease worldwide and accounts for more than 50% of patients on renal replacement therapy programmes.[1,12,23] The mean age of onset of DM found in our study was consistent with the findings by various workers who indicated that type II DM is the predominant form of the disease in this population.[2,15-18]

In agreement with the suggestions of Locatelli and Del Vecchio,[22] socio-economic status assessed in this study using surrogates such as level of education and occupation, was not found to be predictive of nephropathy. This may have been due to the permeating nature of poverty in the semi-urban population of the study. It is, therefore, not surprising that body mass index was not found to be different between our patients with DN and those without. This was earlier reported by Ikem, *et al.*[15]

Duration of *diabetes mellitus* of at least 12 years was shown in this study to portend greater risk for development of DN; the finding is similar to those of others.[15,16,22] This may be because the majority of our diabetic population are type II DM patients who usually present late and have some evidence of nephropathy, hypertension or some other

complications even at presentation.[12,21,30,31]

Hypertension and poor glycaemic control contributed to the development of DN in this study in agreement with other researchers.[15,16,22, 24-27] Persistent hyperglycaemia has been recognised as to leading to glycation of tissue proteins, increased oxidative stress and renal polyol formation, via the aldose reductase pathway, leading to glomerulosclerosis and other microvascular complications. Increased systemic and intraglomerular pressure and activation of various vasoactive hormone pathways have also been implicated in the pathogenesis of diabetic nephropathy. Both haemodynamic and metabolic pathways are now known to independently activate intracellular second messengers such as protein kinase C, MAP kinase, nuclear transcription factors (NF-kappa B) and various growth factors. This ultimately leads to increased renal albumin permeability and extracellular matrix accumulation, with resulting proteinuria, glomerulosclerosis and tubulointerstitial fibrosis.[32-34]

Cigarette smoking is known to exacerbate renal injury in diabetic nephropathy and its cessation in those with microalbuminuria ameliorates the progressive renal injury.[24,33] This study did not find cigarette smoking to be an important discriminator between our subset of DN subjects and diabetics without nephropathy, as very insignificant numbers had a history of smoking, and in addition it was occasional in them. This might be explained by the cultural characteristics of the local population where smoking is regarded as almost a taboo. In contrast, cigarette smoking is a major health risk in the western world and contributes significantly to progression of DN.[22,24,33]

It is noteworthy that the mean creatinine clearance in the studied population was quite low suggesting an early onset of CRF. It has been reported that a sizeable number of patients have complications of DM at the time of diagnosis of DN, such as peripheral neuropathy, eye disease and ischaemic heart disease.[12,15,16,21] The finding of these complications suggests a common pathogenetic mechanism with nephropathy. It is, therefore, not surprising that we found diabetic retinopathy and peripheral neuropathy in 80.9% and 86.7% of the subjects respectively. In addition, they were significantly more common in studied subjects than in controls.

Intriguingly, total serum cholesterol levels did not differ significantly between patients and controls; though the different serum lipid fractions which may have revealed any form of dyslipidaemia were not assessed. This is being unravelled by an ongoing study.

The limitations of this study included its being hospital based and the fact that it examined diabetic subjects with overt nephropathy, as determined by positive urinary dipstick for proteinuria, and compared them with those without overt proteinuria. Subjects with microalbuminuria who are actually in incipient nephropathy may have been included in controls.

In conclusion, the risk factors promoting the development of nephropathy in Nigerian diabetics are similar in many respects to those of the western world. Even though factors such as hypertension, poor glycaemic control and long duration of DM were uncovered in this study, others such as cigarette smoking and obesity (increased BMI) were not found to be discriminant factors. Our preventive strategies should include adequate control of blood pressure, maintenance of euglycaemia and strict longitudinal follow up of diabetic patients. Early detection and treatment of DN and diseases associated with it will delay the onset of ESRD.

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